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Activation of 1,2- and 1,3-Ketoamides with Thiourea Organocatalyst for the Enantioselective Domino Synthesis of Functionalized Cyclohexanes

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Abstract: Several reactive sites of 1,2- and 1,3-ketoamides were successively exploited in two complementary domino transformations for the synthesis of either polysubstituted mono cyclic or bridged bicyclic cyclohexanes with the creation of up to six stereogenic centers. In both cases, a chiral bifunctional thiourea organocatalyst allowed an efficient control of the chirality in the final carbocycles.

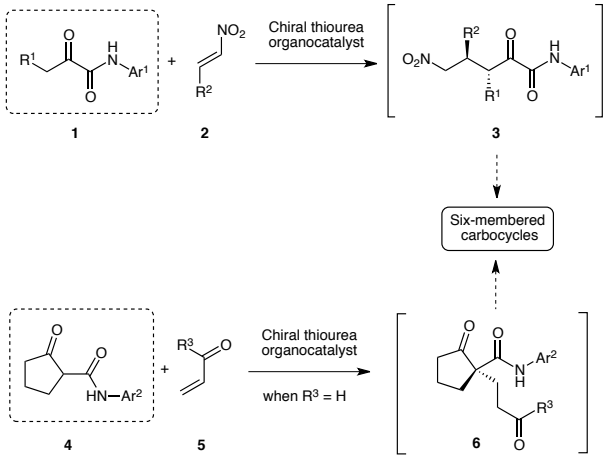
Keywords: Enantioselective organocatalysis, Domino reactions, Ketoamides, Cyclohexanes, Bifunctional thioureas

Introduction

The development of domino enantioselective organocatalytic methodologies has received an intense research attention attested by the high number of recent reports directed to the stereoselective construction of heterocylic and carbocyclic scaffolds.[1] Among these, substituted chiral cyclohexanes are important building blocks in organic synthesis,[2] and many of these approaches have allowed the control of the relative and absolute configurations in the construction of these versatile molecular architectures.[3,4] These methods have the advantage of assembling efficiently the desired target from easily accessible starting materials along with the creation and control of multiple stereogenic carbon atoms. Most of these strategies employ simple substrates with multiple reactive sites that are involved successively in the formation of carbon–carbon and/or carbon–heteroatom bonds. In this context, dicarbonyl compounds and more particularly ketoamides are attractive substrates given the high density of potential reactive sites and thus, they are well suited for designing new stereoselective domino transformations for the asymmetric synthesis of functionalized six-membered carbocycles.[5]

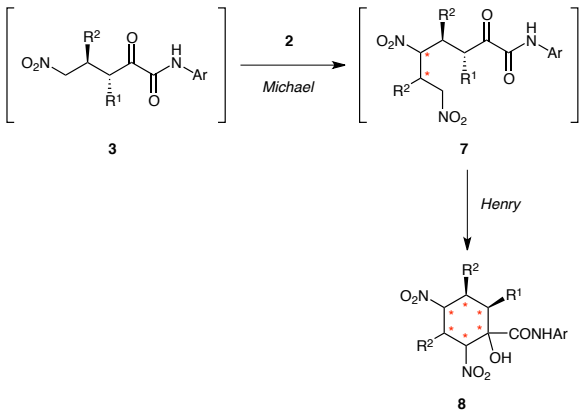
Results and discussion

We have recently shown that 1,2- and 1,3-ketoamides **1** and **4** could be specifically activated using a thiourea-tertiary amine bifunctional organocatalyst and consequently, we successfully developed enantioselective Michael additions with these substrates and either nitroalkenes **2** or α,β-unsaturated carbonyls **5** as the electrophilic partners.[6] We now wish to exploit this work and the Michael adducts **3** and **6** as versatile synthetic platforms in subsequent transformations leading to more complex molecular frameworks, such as substituted cyclohexanes (Scheme 1).



Scheme 1. Access to optically active six-membered carbocycles from 1,2- and 1,3-ketoamides **1** and **4**

In the case of 1,2-ketoamides **1**, and once the Michael adduct **3** is formed (Scheme 2), we reasoned that the addition of a second equivalent of nitroalkene could trigger another conjugate addition leading to intermediate **7**. The latter should then undergo an intramolecular Henry reaction, terminating the domino transformation and affording the desired hexasubstituted cyclohexane **8**.[7]



Scheme 2. Strategy for the synthesis of hexasubstituted cyclohexanes **8**

We started our investigations by screening various bifunctional organocatalysts **I-IV** bearing either

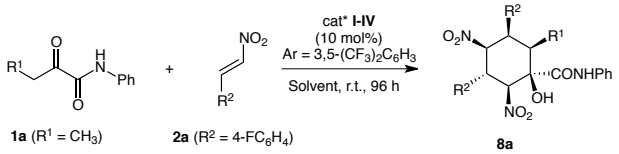
thiourea or squaramide hydrogen-bond donor subunits (Table 1). While catalyst **I** derived from cinchonine allowed only the formation of **8a** as traces (entry 1, the sequence stopped at the Michael adduct stage), we were very pleased to find that Takemoto's catalyst **II** (*R*,*R*-TUC)[8] was efficient for this domino transformation, affording **8a** in good yield (67%) with very good diastereo- and enantiomeric ratios (>20:1 and 28:1 respectively, entry 2). Remarkably, one out of the 64 possible stereoisomers was obtained predominantly. The use of catalysts **III** and **IV** with a squaramide subunit gave poor results (entries 3 and 4) and only trace amounts of cyclohexane **8a** were formed (<5%). The highest yield and stereoselectivities were obtained in ethyl acetate (entry 2) and switching to dichloromethane led to the formation of the desired product in lower yield and selectivities (entry 5). Other solvents such as DMSO and MTBE were not suitable, leading to decomposition and poor reactivity, respectively. (entries 6 and 7).

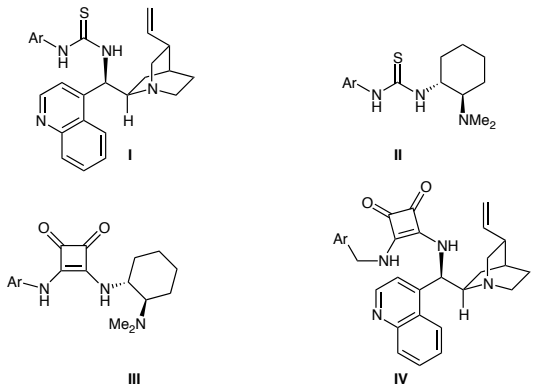
Table 1. Optimization of the domino Michael–Michael–Henry[a]

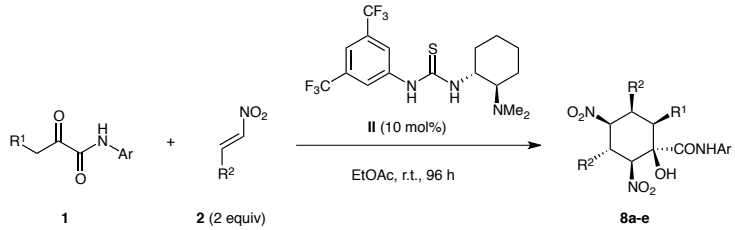
Entry	Catalyst	Solvent	Yield of **8a**[b]	dr[c]	er[d]
1	**I**	EtOAc	<5%	n.d.	n.d.
2	**II**	EtOAc	62%	>20:1	28:1
3	**III**	EtOAc	<5%	n.d.	n.d.
4	**IV**	EtOAc	<5%	n.d.	n.d.
5	**II**	CH_2Cl_2	45%	1:1.5	n.d.
6	**II**	DMSO	decomposition	-	-
7	**II**	MTBE	<5%	n.d.	n.d.

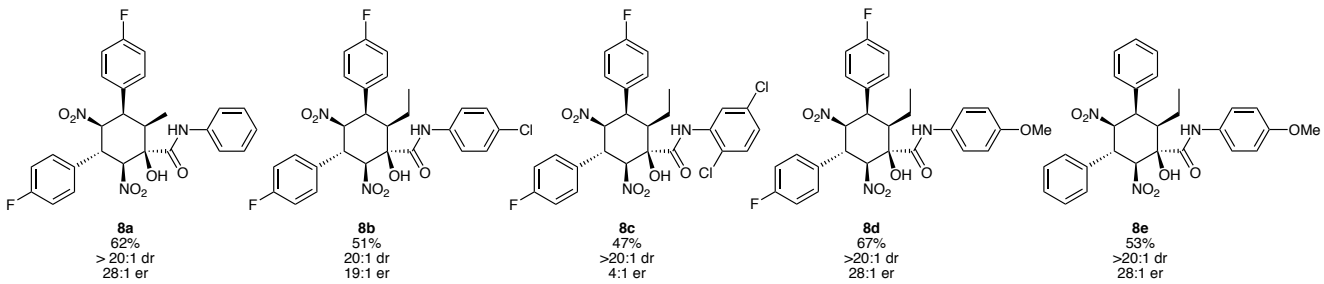
[a]All reactions were run using 0.2 mmol of **1a**, 0.42 mmol of **2a** in 0.4 mL of solvent. [b]Yields of analytically pure isolated products. [c]Diastereomeric ratios were determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixtures. [d]Enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase.

After optimizing the reaction conditions, we studied the possibility of using different ketoamides **1** as well as different nitroalkenes **2** to synthesize various hexasubstituted cyclohexane derivatives **8a-e** (Scheme 3). Hence, using Takemoto's catalyst **II**, in ethyl acetate at room temperature for four days, we were delighted to found that the cyclohexanes **8** were obtained in fair yields but most importantly with generally very good stereoselectivities. Electron-withdrawing as well as electron-donating groups on the aryl substituent of the ketoamide **1** were well tolerated in this reaction, although the use of ketoamide **1c** (R^1 = Et, Ar = 2,5-$Cl_2C_6H_3$) bearing a sterically demanding 2,5-dichlorophenyl substituent had a negative impact on the enantioselectivity of the domino reaction (**8c**, e.r. = 4:1). Concerning the nitroalkene partner **2**, both phenyl- and *p*-fluorophenylnitroalkenes are suitable substrates for this reaction.



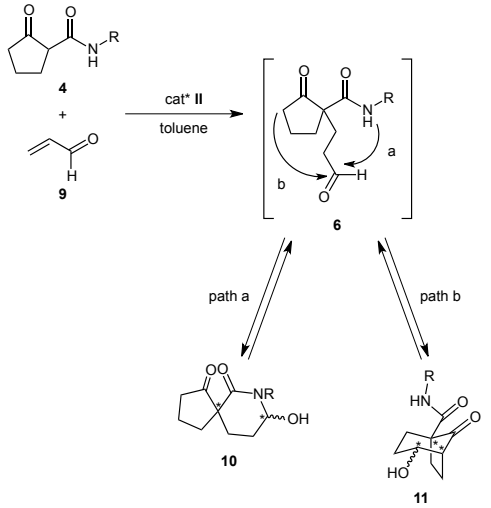






Scheme 3. Scope of the Michael–Michael–Henry reaction leading to **8**

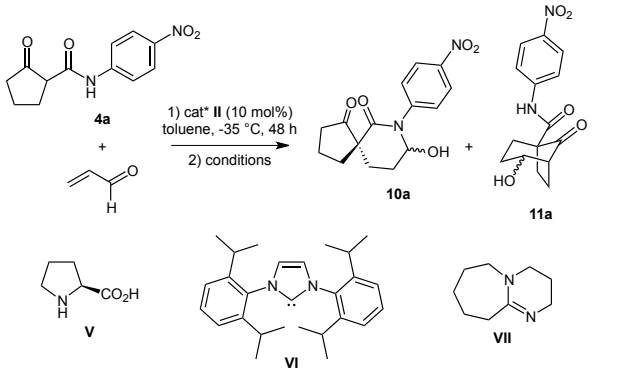
Our earlier studies had shown that Takemoto's catalyst **II** was also efficient to promote the enantioselective Michael addition of 1,3-ketoamides **4** to α,β-unsaturated carbonyls.[6b] When acrolein **9** is used as the electrophilic reaction partner, two modes of cyclization can be envisaged for the initial adducts **6** (Scheme 4). The first one is the formation of hemiaminal **10**, which we already exploited (path a). The second one may involve an intramolecular aldol reaction, leading directly to a bicyclo[3.2.1]octane **11** that bears a bridged six-membered ring with three stereogenic centers (path b). Given the prevalence of this skeleton in natural products and the challenge associated with their synthesis,[9] new modular enantioselective accesses are of high synthetic interest.



Scheme 4. Diverging pathways for the cyclization of the adducts of 1,3-ketoamides with acrolein

In our initial study with *N*-tosylketoamide, the hemiaminal was obtained as the sole product.[6b] However, when we tried to extend this reactivity to *N*-arylketoamide **4a**, a spontaneous evolution towards a mixture of both products **10a** and **11a** was observed (Table 2), indicating that an equilibrium exists between compounds **10a**, which is the kinetic product, and **11a**, which is the thermodynamic one. At −20 °C in the presence of catalyst **II**, after 48 h at room temperature a 3.5:1 ratio between products **10a** and **11a** with the hydroxyl group in axial position was obtained (Entry 1). To favor the formation of the bicyclic product, different reaction conditions were investigated after the completion of the Michael addition. At room temperature, without the addition of any other reagent, a slow evolution was observed to reach a 1.5:1 ratio after an additional two days stirring (Entry 2). We could verify that Takemoto's catalyst **II** was really involved in this process as no interconversion between the products was obtained in its absence. As expected, increasing the temperature to 60 °C led to the formation of **11a** as major compound with a 12:1 dr and a 4.7:1 er (Entry 3). We then looked for other additives that could affect the thermodynamic interconversion of **10a** to **11a**. While the addition of a catalytic amount of L-proline **V** had limited impact (Entry 4), stoichiometric amounts of *N*-heterocyclic carbene IPr **VI** (Entry 5)[10] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **VII** (Entry 6) completely shifted the equilibrium towards the desired product **11a**, albeit with very modest diastereoselectivities. In the last case, the er of the major diastereomer amounted to 5.1:1.

Table 2. Optimization of the reaction conditions for the synthesis of bicyclo[3.2.1]octane **11a**[a]

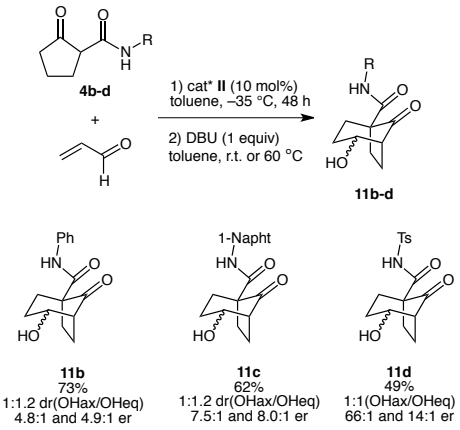


Entry	conditions	ratio **10a**/**11a**[b]	dr (OH_{ax}/OH_{eq})[c]	er[d]
1	-[e]	3.5:1	>20:1	n.d.
2	r.t., 2 d	1.5:1	>20:1	n.d.
3	60 °C, 2 d	1:9.3	12:1	4.7:1
4	**V** (20 mol%), r.t., 2 d	1:1.1	>20:1	n.d.
5	**VI** (1.1 equiv), r.t., 3 d	<1:20	1:2	n.d.
6	**VII** (1 equiv), r.t., 10 min	<1:20[f]	1.4:1	4.1:1 and 3.7:1

[a]All reactions were run using 0.2 mmol of **4a**, 0.4 mmol of **9** in 4 mL of solvent. [b]Determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixtures. [c]Diastereomeric ratios were determined by ^{1}H NMR spectroscopy analysis of the crude reaction mixtures. [d]Enantiomeric ratio of the major diastereomer of **11a** (OH in axial position) was determined by HPLC analysis on a chiral stationary phase. [e]Analyses conducted directly at the end of the Michael addition step. [f] 82% yield after purification.

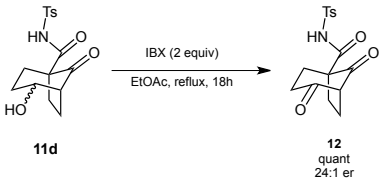
DBU was selected as the best promoter for the isomerization because it allowed an efficient reaction with a short reaction time and we investigated the behavior of other 1,3-ketoamides[11] when submitted to these reaction conditions (Scheme 5). With other *N*-aryl-1,3-ketoamides **4b** and **4c**, we noticed that an evaporation of the excess acrolein was required prior to DBU addition in order to avoid a double Michael addition. Products **11b** and **11c** were obtained with reasonable yields but moderate stereoselectivities. Interestingly, *N*-aryl-1,3-ketoamides **4d** could also be

converted into the bicyclic product **11d**. Because of the higher stability of the hemiaminal in this case, the isomerization with DBU had to be conducted at 60 °C. Once again, there was no diastereoselectivity but high enantioselectivities (66:1 and 14:1 er respectively) were obtained for both diastereomers. The differences in enantiomeric ratios observed between the different cyclization modes[12] clearly indicate that these compounds are prone to racemization. As a result, particular care must be taken during the reaction and post functionalization to avoid such an issue.



Scheme 5. Scope study of the formation of bicyclo[3.2.1]octanes **11**

Bicyclic alcool **11d** could also be derivatized with success by IBX oxidation in refluxing ethyl acetate, quantitatively generating the bicyclo[3.2.1]octanedione **12** (Scheme 6). Most importantly, an excellent 24:1 er was observed for the formation of this valuable structure.



Scheme 6. Scope study of the formation of bicyclo[3.2.1]octanes **11**

Conclusion

We have demonstrated that 1,2- and 1,3-ketoamides could be specifically activated with thiourea organocatalysts and used in domino transformations for the enantioselective synthesis of polysubstituted cyclohexanes. In the case of 1,2-ketoamides, we exploited both their pronucleophilic character,[13] and the ketone moiety as electrophile site for the synthesis of hexasusbtituted cyclohexanes by reaction with nitroalkenes partners. Amazingly, one out of 64 stereoisomers was formed almost exclusively. Alternatively, 1,3-ketoamides where used as efficient *C*-bisnucleophiles with acroleine as the electrophilic partner allowing access to bicyclo[3.2.1]octanes in the optically active form with the formation of two new *C–C* bonds and three stereogenic carbon atoms. Further studies are currently undertaken in our laboratory in order to extend the scope of these promising cascade reactions.

Experimental section

All reagents were obtained from commercial sources and used as supplied unless otherwise stated. NMR data were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ and chemical shifts (δ) are given in ppm relative to the residual non-deutered solvent signal for ^{1}H NMR ($CHCl_3$: 7.26 ppm), and relative to the deutered solvent signal for ^{13}C NMR ($CDCl_3$: 77.16 ppm); coupling constants (J) are in Hertz, and the classical abbreviations are used to describe the signal multiplicity. High-resolution mass spectra were obtained from the Spectropole (http://www.spectropole.u-3mrs.fr/). Optical rotations were measured with a PERKIN ELMER 241 micropolarimeter. Melting points (mp) were determined with a Büchi Melting-point B-450 apparatus and were not corrected. Thin layer chromatography (TLCs) were developed on silica *Merck 60F$_{254}$*. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with phosphomolybdic acid and *p*-anisaldehyde reagents. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230-400 mesh).

General procedure for the synthesis of cyclohexanes 8

1,2-ketoamides **1** (1.00 equiv), nitroalkenes **2** (2.10 equiv) and thiourea-catalyst **II** (0.10 equiv) were successively added as solid in a sealed tube and dissolved in ethyl acetate (0.5 M). After 96 hours of reaction time at room temperature, the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 30:70 then 50:50). The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy analysis of the crude product and the enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase.

8a: this product was synthesized starting from **1a** (R^1 = Me, Ar = Ph, 36 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4, 70 mg, 0.42 mmol) according to the above procedure and was obtained as a white solid (63 mg, 62%). R*f* (EA/PE, 3:7) = 0.30; mp = 181-182 °C; α_D^{30} (CH_2Cl_2, *c* = 1.0) = –22.3; Chiral HPLC (ChiralPak AD-H, hexane/*i*PrOH = 9:1, flow rate = 1.0 mL/min, λ = 306 nm): t_{minor} = 24.7 min, t_{major} = 28.0 min, er = 99:1; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.65 (brs, 1H, NH), 7.62 (br s, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.42-7.36 (m, 4H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 5.76 (d, *J* = 12.0 Hz, 1H), 5.60 (dd, *J* = 12.0, 7.2 Hz, 1H), 4.61 (dd, *J* = 12.0, 12.0 Hz, 1H), 4.61 (s, 1H, OH), 4.00

(dd, J = 7.2, 7.2 Hz, 1H), 3.05–2.99 (m, 1H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 169.1, 163.4 (d, J = 248 Hz), 163.3 (d, J = 248 Hz), 138.8 (d, J = 8 Hz, 2C), 136.7 (2C), 130.5 (d, J = 8 Hz, 2C), 129.9 (d, J = 4 Hz), 129.7, 129.5 (d, J = 4 Hz), 126.1, 120.7 (2C), 116.8 (d, J = 17 Hz, 2C), 115.7 (d, J = 17 Hz, 2C), 92.0, 89.3, 80.1, 49.7, 42.2, 39.3, 14.0; HRMS (ES+): m/z calcd for $[(C_{26}H_{24}F_2N_3O_6+H)^+]$: 512.1628; found: 512.1619.

8b: this product was synthesized starting from **1b** (R^1 = Et, Ar = 4-ClC_6H_4, 45 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4, 70 mg, 0.42 mmol) according to the above procedure and was obtained as a white solid (57 mg, 51%). mp 248 °C (dec.). R*f* (EA/PE, 1:4) = 0.30; Chiral HPLC (ChiralPak IA, hexane/ethanol/chloroforme = 5:3:2, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 4.0 min, t_{major} = 5.8 min, er = 19:1; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.68 (brs, 1H, NH), 7.70 (br s, 2H), 7.50 (d, J = 8.9 Hz, 2H), 7.37-7.31 (m, 4H), 7.08 (d, J = 8.9 Hz, 2H), 7.03 (d, J = 8.9 Hz, 2H), 5.61 (d, J = 12.5 Hz, 1H), 5.43 (dd, J = 12.5, 6.9 Hz, 1H), 4.65 (s, 1H, OH), 4.45 (dd, J = 12.5, 12.5 Hz, 1H), 4.16 (dd, J = 6.9, 6.9 Hz, 1H), 2.75-2.70 (m, 1H), 1.44-1.33 (m, 2H), 0.87 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 169.3, 163.2 (d, J = 248 Hz), 163.1 (d, J = 248 Hz), 135.3, 133.8 (d, J = 8 Hz, 2C), 130.9, 130.4 (d, J = 8 Hz, 2C), 129.7 (d, J = 4 Hz), 129.6 (2C), 129.0 (d, J = 4 Hz), 121.9 (2C), 116.7 (d, J = 22 Hz, 2C), 115.8 (d, J = 22 Hz, 2C), 92.1, 89.8, 80.2, 46.7, 46.1, 41.6, 20.8, 12.0; MS (ES+): m/z $[(M+Na)^+]$ 582; HRMS (ES+): m/z calcd for $[(C_{27}H_{24}N_3O_6ClF_2+H)^+]$: 560.1394; found: 560.1395.

8c: this product was synthesized starting from **1c** (R^1 = Et, Ar = 2,5-$Cl_2C_6H_3$, 52 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4, 70 mg, 0.42 mmol) according to the above procedure and was obtained as a white solid (57 mg, 47%). R*f* (EA/PE, 1:4) = 0.41; mp = 203-205 °C; α_D^{22} (CH_2Cl_2, *c* = 0.52) = –12.9; Chiral HPLC (ChiralPak IA, hexane/ethanol/chloroforme = 3:1:1, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 4.1 min, t_{major} = 5.8 min, er = 4 : 1; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 9.21 (brs, 1H, NH), 8.35 (brs, 1H), 7.72-7.69 (m, 2H), 7.38-7.34 (m, 4H), 7.14-7.04 (m, 5H), 5.56 (d, J = 12.5 Hz, 1H), 5.39 (dd, J = 12.5, 6.8 Hz, 1H), 4.72 (s, 1H, OH), 4.46 (dd, J = 12.5, 12.5 Hz, 1H), 4.17 (dd, J = 6.8, 6.8 Hz, 1H), 2.72-2.67 (m, 1H), 1.55-1.37 (m, 2H), 0.88 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 169.5, 163.3 (d, J = 248 Hz), 163.2 (d, J = 248 Hz), 134.4, 133.8 (d, J = 8 Hz, 2C), 130.5 (2C), 130.4 (d, J = 8 Hz), 129.6 (d, J = 4 Hz), 128.9 (d, J = 4 Hz), 126.4, 122.6, 121.8, 116.7 (d, J = 22 Hz, 2C), 115.9 (d, J = 22 Hz, 2C), 92.1, 89.8, 80.5, 46.7, 46.2, 41.6, 20.7, 12.0; MS (ES+): m/z $[(M+Na)^+]$ 616; HRMS (ES+): m/z calcd for $[(C_{27}H_{23}N_3O_6Cl_2F_2+H)^+]$: 594.1005; found: 594.1003.

8d: this product was synthesized starting from **1d** (R^1 = Et, Ar = 4-$MeOC_6H_4$, 44 mg, 0.2 mmol) and **2a** (R^2 = 4-FC_6H_4, 70 mg, 0.42 mmol) according to the above procedure and was obtained as a white solid (74 mg, 67%). R*f* (EA/PE, 1:4) = 0.11; mp = 109-111 °C; α_D^{30} (CH_2Cl_2, 0.57) = +29.5; Chiral HPLC (ChiralPak IB, hexane/ethanol = 4:1, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 10.9 min, t_{major} = 6.6 min, er = 28:1; ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.60 (brs, 1H, NH), 7.69-7.66 (m, 2H), 7.41 (d, J = 9.0 Hz, 2H), 7.34-7.30 (m, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.70 (d, J = 12.3 Hz, 1H), 5.50 (dd, J = 12.3, 6.9 Hz, 1H), 4.69 (s, 1H, OH), 4.41 (dd, J = 12.3, 12.3 Hz, 1H), 4.11 (dd, J = 6.9, 6.9 Hz, 1H), 2.82-2.76 (m, 1H), 1.47-1.36 (m, 2H), 0.87 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 168.7, 162.8 (d, J = 248 Hz), 162.7 (d, J = 248 Hz), 157.5, 133.2 (d, J = 8 Hz, 2C), 129.9 (d, J = 8 Hz, 2C), 129.0 (d, J = 4 Hz), 128.9, 128.5 (d, J = 4 Hz), 122.0 (2C), 116.3 (d, J = 22 Hz, 2C), 115.6 (d, J = 22 Hz, 2C), 114.4 (2C), 91.7, 89.3, 79.7, 55.5, 46.4, 45.5, 41.2, 20.3, 11.8; MS (ES+): m/z $[(M+Na)^+]$ 579; HRMS (ES+): m/z calcd for $[(C_{28}H_{27}N_3O_7F_2+H)^+]$: 556.1890; found: 556.1889.

8e: this product was synthesized starting from **1d** (R^1 = Et, Ar = 4-$MeOC_6H_4$, 44 mg, 0.2 mmol) and **2b** (R^2 = C_6H_5, 63 mg, 0.42 mmol) according to the above procedure and was obtained as a white solid (55 mg, 53%). R*f* (EtOAc/PE, 1:4) = 0.18; mp = 139-141 °C; α_D^{22} (CH_2Cl_2, *c* = 9.9) = +9.7; Chiral HPLC (ChiralPak IB, exane/ethanol = 7:3, flow rate = 1.0 mL/min, λ = 254 nm): t_{minor} = 6.6 min, t_{major} = 5.3 min, er = 28:1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (brs, 1H, NH), 7.69 (br s, 2H), 7.40-7.36 (m, 8H), 7.34-7.28 (m, 2H), 6.86 (d, J = 9.0 Hz, 2H), 5.69 (d, J = 12.5 Hz, 1H), 5.48 (dd, J = 12.5, 6.7 Hz, 1H), 4.54 (dd, J = 12.5, 12.5 Hz, 1H), 4.52 (s, 1H, OH), 4.13 (dd, J = 6.7, 6.7 Hz, 1H), 3.77 (s, 3H), 2.81-2.76 (m, 1H), 1.45-1.37 (m, 2H), 0.91 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 157.3, 133.7, 132.9 (2C), 131.3 (2C), 129.2 (2C), 129.0, 128.7 (2C), 128.6, 128.2 (2C), 122.0 (2C), 114.3 (2C), 92.0, 89.4, 79.7, 55.5, 47.0, 45.7, 41.9, 20.4, 11.9. MS (ES+): m/z $[(M+Na)^+]$ 542; HRMS (ES+): m/z calcd for $[(C_{28}H_{29}N_3O_7+H)^+]$: 520.2078; found: 520.2077.

General procedure for the synthesis of bicyclo[3.2.1]octanes 11

A solution of 1,3-ketoamides **4** (0.2 mmol, 1 equiv) and thiourea-catalyst **II** (0.02 mmol, 0.1 equiv.) in dry toluene (4 mL) was cooled at –35°C. Acrolein **9** (27 µL, 0.4 mmol, 2 equiv) was added and the mixture was stirred for 24-48 hours until full conversion of **4**. Then DBU (30 µL, 0.2 mmol, 1 equiv.) was added to the reaction medium, which was subsequently warmed to room temperature and stirred for 1 hour. The mixture was concentrated under reduced pressure. HCl (1N) was added and the mixture was extracted twice with CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product

was purified by flash column chromatography (ethyl acetate/petroleum ether) to afford pure **11**.

11a: this product was synthesized starting from **4a** (R = 4-$NO_2C_6H_4$, 50 mg, 0.2 mmol) according to the above procedure and was obtained as a 1.4:1 mixture of diastereomers as a pale yellow solid (50 mg, 82%). R*f* (EA/CH_2Cl_2, 2:3) = 0.33; mp = 137-139 °C; Chiral HPLC (Lux-Amylose-2, hexane/*i*PrOH = 7:3, flow rate = 1.0 mL/min, λ = 220 nm): diastereomer OH_{ax}: t_{minor} = 18.0 min, t_{major} = 21.0 min, er = 4.1:1, diastereomer OH_{eq}: t_{minor} = 10.1 min, t_{major} = 11.3 min, er = 3.7:1; ^{1}H NMR (400 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 10.21 (s, NH), 8.21 (d, *J* = 9.2 Hz, 2H), 7.77 (d, *J* = 9.2 Hz, 2H), 4.45 (s, 1H), 2.67 (dd, *J* = 7.1, 5.4 Hz, 1H), 2.46-2.40 (m, 1H), 2.39-2.31 (m, 2H), 2.31-2.12 (m, 2H), 2.03-1.92 (m, 1H), 1.84-1.71 (m, 2H), diastereomer OH_{eq}: δ 10.07 (s, NH), 8.21 (d, *J* = 9.2 Hz, 2H), 7.77 (d, *J* = 9.2 Hz, 2H), 4.14 (br s, 1H), 2.75 (dd, *J* = 7.0, 3.1 Hz, 1H), 2.46-2.40 (m, 1H), 2.39-2.31 (m, 2H), 2.31-2.12 (m, 2H), 2.03-1.92 (m, 1H), 1.84-1.71 (m, 2H). ^{13}C NMR (75 MHz, DMSO-*d*6): diastereomer OH_{ax}: δ 213.0, 171.0, 145.42, 142.21, 124.88 (2C), 119.3 (2C), 76.9, 57.5, 52.3, 34.1, 26.6, 25.4, 18.9, diastereomer OH_{eq}: δ 213.1, 170.7, 145.36, 142.23, 124.94 (2C), 119.2 (2C), 73.6, 57.7, 54.8, 31.8, 28.2, 26.4, 16.3; MS (ES+): m/z [$(M+Na)^+$] 327; HRMS (ES+): m/z calcd for [$(C_{15}H_{16}N_2O_5+H)^+$]: 305.1132; found: 305.1130.

11b: this product was synthesized starting from **4b** (R = C_6H_5, 41 mg, 0.2 mmol) by adapting the above procedure. After full conversion of **4b**, the excess of acrolein was eliminated by reduced pressure (100 mbar), without evaporation of toluene. Then DBU was added and the reaction mixture was stirred at room temperature for 1 hour to afford **11b** as a 1:1.2 mixture of diastereomers as a colorless viscous liquid (38 mg, 73%). R*f* (EA/CH_2Cl_2, 2:3) = 0.28; Chiral HPLC (Chiralcel OD-3, hexane/*i*PrOH = 9:1, flow rate = 1.0 mL/min, λ = 254 nm): diastereomer OH_{ax}: t_{minor} = 18.9 min, t_{major} = 23.0 min, er = 4.8:1, diastereomer OH_{eq}: t_{minor} = 17.0 min, t_{major} = 20.4 min, er = 4.9:1; ^{1}H NMR (400 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 9.79 (s, NH), 7.60-7.51 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (td, *J* = 7.3, 1.2 Hz, 1H), 4.42-4.30 (m, 1H), 2.64-2.57 (m, 1H), 2.44-2.19 (m, 4H), 2.16-1.99 (m, 1H), 1.96-1.64 (m, 3H), diastereomer OH_{eq}: δ 9.67 (s, NH), 7.60-7.51 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.10 (td, *J* = 7.3, 1.2 Hz, 1H), 4.18-4.03 (m, 1H), 2.72 (dd, *J* = 6.9, 3.2 Hz, 1H), 2.44-2.19 (m, 3H), 2.16-1.99 (m, 2H), 1.96-1.64 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 217.9, 170.0, 137.7, 129.1 (2C), 124.5, 120.3 (2C), 78.5, 54.4, 53.2, 38.5, 26.3, 25.8, 18.6, diastereomer OH_{eq}: δ 216.9, 169.9, 137.6, 129.1 (2C), 124.6, 120.3 (2C), 74.7, 55.2, 53.9, 35.6, 27.5, 26.7, 15.5. MS (ES^+): m/z [$(M+Na)^+$] 282; HRMS (ES+): m/z calcd for [$(C_{15}H_{17}NO_3+H)^+$]: 260.1281; found: 260.1284.

11c: this product was synthesized starting from **4c** (R = 1-naphthyl, 51 mg, 0.2 mmol) by adapting the above procedure. After full conversion of **4c**, the excess of acrolein was eliminated by reduced pressure (100 mbar), without evaporation of toluene. Then DBU was added and the reaction mixture was stirred at room temperature for 1 hour to afford **11c** as a 1:1.2 mixture of diastereomers as a viscous liquid (38 mg, 62%). R*f* (EA/CH_2Cl_2, 2:3) = 0.30; Chiral HPLC (Lux-Amylose-2, hexane/*i*PrOH = 7:3, flow rate = 1.0 mL/min, λ = 254 nm): diastereomer OH_{ax}: t_{minor} = 10.2 min, t_{major} = 33.5 min, er = 7.5:1, diastereomer OH_{eq}: t_{minor} = 6.9 min, t_{major} = 7.9 min, er = 8.0:1; ^{1}H NMR (400 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 10.38 (s, NH), 8.18-8.12 (m, 2H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.61-7.55 (m, 1H), 7.54-7.44 (m, 2H), 4.41-4.30 (m, 1H), 2.64 (dd, *J* = 7.1, 5.2 Hz, 1H), 2.55-2.21 (m, 4H), 2.20-2.07 (m, 1H), 1.88-1.65 (m, 3H), diastereomer OH_{eq}: δ 10.24 (s, NH), 8.18-8.12 (m, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.61-7.55 (m, 1H), 7.54-7.44 (m, 2H), 4.17-4.04 (m, 1H), 2.76 (dd, *J* = 6.9, 3.2 Hz, 1H), 2.55-2.21 (m, 3H), 2.20-2.07 (m, 1H), 2.06-1.89 (m, 2H), 1.88-1.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 170.5, 134.2, 132.6, 128.8, 126.6, 126.5, 126.1, 125.8, 125.3, 120.9, 119.3, 78.7, 54.9, 53.2, 38.9, 26.4, 25.9, 18.7, diastereomer OH_{eq}: δ 217.6, 170.3, 134.2, 132.5, 128.8, 126.6, 126.5, 126.1, 125.8, 125.3, 120.7, 119.4, 74.8, 55.2, 54.4, 35.9, 27.6, 26.8, 15.6. MS (ES^+): m/z [$(M+Na)^+$] 332; HRMS (ES+): m/z calcd for [$(C_{19}H_{19}NO_3+H)^+$]: 310.1438; found: 310.1443.

11d: this product was synthesized starting from **4d** (R = Ts, 56 mg, 0.2 mmol) by adapting the above procedure. After addition of DBU, the reaction mixture was heated at 60 °C for 6 hours to afford **11d** as a 1:1 mixture of diastereomers as a viscous liquid (33 mg, 49%). R*f* (EA/CH_2Cl_2, 2:3) = 0.55; Chiral HPLC (Chiralpak IC, hexane/*i*PrOH/TFA = 7:3:0.01, flow rate = 1.0 mL/min, λ = 254 nm): diastereomer OH_{ax}: t_{minor} = 45.6 min, t_{major} = 48.3 min, er = 66:1, diastereomer OH_{eq}: t_{minor} = 26.6 min, t_{major} = 32.6 min, er = 14:1; ^{1}H NMR (400 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 10.23 (s, NH), 7.93 (d, *J* = 8.4, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.36 (d, *J* = 1.7 Hz, 1H), 2.60 (dd, *J* = 6.9, 5.5 Hz, 1H), 2.42 (s, 3H), 2.35-2.26 (m, 1H), 2.15-1.98 (m, 4H), 1.92-1.64 (m, 3H), diastereomer OH_{eq}: δ 10.12 (s, NH), 7.93 (d, *J* = 8.4, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.10-4.07 (m, 1H), 2.70 (dd, *J* = 6.9, 3.2 Hz, 1H), 2.42 (s, 3H), 2.35-2.26 (m, 1H), 2.15-1.98 (m, 4H), 1.92-1.64 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): diastereomer OH_{ax}: δ 216.0, 169.4, 145.1, 135.8, 129.7 (2C), 128.5 (2C), 78.2, 55.5, 52.5, 37.9, 26.4, 25.5, 21.8, 18.6, diastereomer OH_{eq}: δ 215.1, 169.4, 145.2, 135.7, 129.7 (2C), 128.5 (2C), 74.4, 55.1, 54.5, 35.1, 26.6, 25.4, 21.8, 15.6. HRMS (ES+):

m/z calcd for [($C_{16}H_{19}NO_5S$+H)$^+$]: 338.1057; found: 338.1061.

12: a solution of **11d** (0.2 mmol, 1 equiv.), and 2-iodoxybenzoic acid (IBX) (0.4 mmol, 2 equiv) in ethyl acetate (1 mL) was refluxed in a sealed tube for 18 hours. After cooling to room temperature, the mixture was filtered through a short pad of Celite® and was concentrated under reduced pressure to afford quantitatively the crude ketone **12**, which could not be further purified because of its instability on silica gel. R*f* (EA/PE, 1:3) = 0.22; Chiral HPLC (Chiralpak IC, hexane/EtOH/TFA = 8:2:0.01, flow rate = 1.0 mL/min, λ = 254 nm): t_{major} = 12.1 min, t_{minor} = 13.9 min, er = 24:1; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.35 (d, *J* = 6.8 Hz, 1H), 2.79 (ddd, *J* = 17.0, 12.6, 9.4 Hz, 1H), 2.50 (dd, *J* = 17.0, 6.7 Hz, 1H), 2.45-2.37 (m, 1H), 2.42 (s, 3H), 2.28-2.10 (m, 3H), 1.97 (ddd, *J* = 14.3, 8.0, 3.1 Hz, 1H), 1.84-1.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.0, 203.5, 168.3, 145.3, 135.5, 129.7 (2C), 128.5 (2C), 64.9, 56.1, 33.6, 30.4, 26.2, 21.8, 21.2. MS (ES$^+$): m/z [(M+Na)$^+$] 358; HRMS (ES+): m/z calcd for [($C_{16}H_{17}NO_5S$+H)$^+$]: 336.0900; found: 336.0898.

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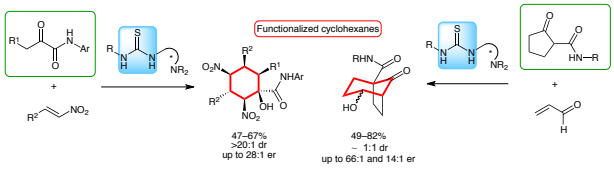
Abstract :



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